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REPLY

We greatly appreciate the comments of our colleagues and recognize that the issue of genetic testing is controversial both in pediatric cardiology and other fields of medicine. We believe that in the case of the 22q11 deletion, the controversy centers on two issues: 1) the utility of early screening and diagnosis, and 2) the ability to identify by clinical exam alone those patients at risk for having a 22q11 deletion.

It is clinically important to identity the patient with the 22q11 deletion in infancy for several reasons. First, the infant recognized to have the deletion is at risk for multiple extracardiac anomalies that warrant early detection and intervention. These include palatal abnormalities, feeding disorders, hypocalcemia, immune deficiencies, renal anomalies, and speech and learning disabilities (1,2). Many of these abnormalities are not apparent on examination alone but are only identified by specialized tests. Although all patients with congenital heart disease should be examined carefully for noncardiac features, infants with a 22q11 deletion are at risk for known anomalies that are best managed by early identification and intervention.

It is also important to identify the infant with a 22q11 deletion for family counseling purposes. Approximately 8% to 28% of cases are familial in origin. Most affected parents are not diagnosed as deletion positive until their child is diagnosed (2,3). The parent with a deletion carries a 50% chance of passing the deletion-bearing chromosome to additional offspring. Although one cannot predict the outcome for the fetus that inherits the deletion bearing chromosome, appropriate monitoring and counseling can be offered to the family because many affected infants have severe forms of heart disease that carry significant morbidity and mortality (1,2). Thus, screening neonates with specific cardiac defects for a 22q11 deletion assures that familial cases will be identified and that appropriate counseling will be offered.

A separate controversy concerns the ability to diagnose the 22q11 deletion syndrome clinically at birth. We agree that subtle dysmorphic features in patients with a 22q11 deletion can often eventually be recognized, particularly in the school-age child. Therefore, in the conclusion of our paper, we recommend testing for a 22q11 deletion in the school-age child with a conotruncal defect only in the presence of additional syndromic features.

However, our experience and published experience demonstrates that subtle clinical features of the 22q11 deletion syndrome may not be apparent in infancy, when we believe the diagnosis should ideally be made. For example, Dr. Digilio and her colleagues report five infants whom they had initially considered to have isolated cardiac defects until reexamination showed otherwise (4). In two of their cases, syndromic features were not recognized until after the deletion was detected and the infants reexamined (5). Therefore, even experienced dysmorphologists can "overlook" subtle syndromic features in the infant.

Given the high frequency of 22q11 deletions in patients with interrupted aortic arch type B, truncus arteriosus and tetralogy of Fallot (TOF) with additional aortic arch or vessel anomalies, routine testing would seem to be less controversial in this cohort of infants (6). The question remains whether testing the infant with TOF and a normal left aortic arch is necessary or can be clinically determined. Additional studies are likely to answer this question more precisely. However, since identification of the syndromic infant is likely to depend upon the experience of the

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examiner, and because laboratory screening may prove to be less expensive than repeated examination by medical specialists (particularly as less expensive PCR based screening assays are put to clinical use) (7), we believe that routine testing of this population can also be justified.

Testing in infancy can avoid the frustration that families often experience as they try to understand why the cardiac defect occurred, whether it will recur in subsequent pregnancies and whether other clinical problems, such as feeding disorders, relate to the cardiac disease. The 22q11 deletion syndrome provides parents with a unifying diagnosis and can preempt visits to different sub-specialists in search of new diagnoses. Most importantly, we hope that this discussion will heighten physicians' awareness of the 22q11 deletion syndrome. Until more conclusive cost benefit analyses and clinical studies can better define appropriate screening guidelines, the decision to test for a 22q11 deletion in the cardiac patient must be considered by each physician according to the facilities and expertise available to them.

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Role of Nitric Oxide in Venous and Arterial Graft Failure

We read with interest the paper from Chello et al. (1) reporting greater neutrophil adhesion in segments of human saphenous vein (SV) than internal mammary artery (IMA), which they ascribed to different endothelial nitric oxide (NO) formation in the two vessels. This, according to the authors, explains the superior early and long-term patency of the IMA as a conduit for coronary artery bypass surgery (CABG) when compared with the SV. Although we agree that the IMA is a preferable conduit, and that the SV produces less endothelial NO than arteries (2), we have a number of concerns over the methodology as well as the clinical implications of this study.

First, the authors presented no data as to the amount of endothelium present in the SV or IMA segments investigated. In our experience, this can be very variable and despite precautions taken at harvesting, there is always some degree of endothelial loss induced by buffers, constriction, dissection and mounting in culture plates. Because this could vary between artery and vein, quantitating endothelial loss should be essential. The evidence that the neutrophils adhered to endothelial cells (and not subendothelium) because less NO is released by SV compared with IMA was that vessels pretreated with sodium nitroprusside or L-arginine reversed the adhesion of neutrophils whereas L-NAME enhanced it. However, the concentrations of the agents used was very high (1–10 mM). Because these drugs are taken up into the interstitial space of vessel segments, they are probably released subsequently into the fluid containing the neutrophils and therefore affect the neutrophils directly. For example, nitroprusside stimulates cyclic GMP formation at 100 nM, which is 1/10,000th lower than the concentration used by Chello et al. One way around these above uncertainties would be to remove the endothelium by rubbing and then to assess neutrophil adhesion using the same treatments as for "intact" segments.

The overall question raised by this study is what role endothelial NO plays in early or late vein graft failure. In a study on porcine vein grafts, removal of the endothelium result in early thrombotic occlusion (3) but had no effect on neointima formation, supporting the idea that exposure of the subendothelium, per se, and not endothelial NO formation, is important in early thrombosis. In the same model, endothelial NO synthase (eNOS) in SV grafts, although initially low, is rapidly upregulated to similar levels of arterial eNOS within one month (2).

Finally, it follows from the study of Chello et al. (1) that the early administration of NO-donors may be beneficial in obviating graft failure in CABG. However, this should be approached with caution because NO elicits several potentially dangerous effects, including apoptosis of endothelial cells, promotion of VSMC proliferation and reactions with